SCIENTIFIC ABSTRACT

We propose initial studies in humans with the long term goals of using gene transfer techniques for the treatment of patients with acute lung injury (adult respiratory distress syndrome--ARDS) and patients with alpha-1 antitrypsin (AAT) deficiency. We propose to use cationic liposomes to deliver a plasmid DNA construct with the cDNA for human alpha-1 antitrypsin driven by a cytomegalovirus promoter. Two different patient protocols are proposed using the exact same DNA and liposome preparations. In patients scheduled for elective pulmonary resection, we will instill plasmid/liposome complexes into a subsegment of the lung to be removed through a fiberoptic bronchoscope and obtain samples of the transfected portion and of the non-transfected portion of the lungs at the time of surgery. By immunohistochemistry, in situ hybridization, western and northern analysis, we will assess the amount and location of transgene expression in the lungs. Histological studies will also determine the effects of the intervention on lung structure. In patients with alpha-1 antitrypsin deficiency, we will instill plasmid/liposome complexes into one nostril and take serial nasal lavages from each nostril, measuring alpha-1 antitrypsin by ELISA in the lavage samples to assess expression of the AAT transgene. Cells obtained by nasal scraping will also be examined by immunohistochemical staining and in situ hybridization to assess transgene expression. Histological appearance of the cells will provide information about effects of the intervention on nasal epithelial cell structure. Because proteolytic events, principally a consequence of the inflammatory process, appear to be important in the pathogenesis of acute lung injury and of chronic pulmonary disease in patients with AAT deficiency (emphysema), development of safe and efficacious systems for delivering the AAT gene to respiratory tract cells might provide a new form of therapy for patients with these diseases.